

Controversy and progress for treatment of acute cholangitis after Tokyo Guidelines (TG13)

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Summary Tokyo Guideline 2013 (TG13) is an international guideline for the diagnosis, classification and treatment of acute cholangitis. Progress and controversy for the two years after TG13 was summarized. Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) are both effective imaging tests for common bile duct (CBD) stones. More factors *e.g.* obesity may be involved in severity assessment. Initiation of broad-spectrum antibiotics addressing the typical Gram-negative enteric bacteria spectrum and early biliary drainage are the mainstay therapeutic options. Early laparoscopic exploration is also an option for stone-related nonsevere acute cholangitis besides endoscopic retrograde cholangial or percutaneous transhepatic cholangial drainage. Surgical biliary drainage should be avoided in severe cholangitis.

Keywords: Acute cholangitis, Tokyo guideline 2013 (TG13), endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), laparoscopic common bile duct exploration (LCBDE)

1. Introduction

Gallstone disease estimates are about 20% in European and Northern American populations. Common bile duct (CBD) stones are estimated to be in 10-20% of individuals with symptomatic gallstone disease (1).

Acute bacterial cholangitis is a common surgical emergency in the spectrum of acute biliary infection with high mortality rates. Thus, there is a need for straightforward diagnostic evaluation and immediate treatment initiation. With this background, Tokyo Guideline derived from international meetings in 2007 (2) and updated in 2013 (3) was published for the diagnosis, classification and treatment of acute cholangitis. Here, we summarize some progress and controversial issues after Tokyo Guideline 2013 (TG13).

2. Imaging diagnosis

There are various modalities available for imaging of the biliary tract. The most powerful is endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP). Trans-abdominal ultrasound still has its role as a first imaging test in initial evaluation due to its wide availability. In the emergency ward, despite its low sensitivity in CBD stone detection ranges from 25 to 63% (4). Yet, ultrasound has high diagnostic accuracy in the demonstration of biliary dilatation. It has to be kept in mind that a definition of biliary dilatation is not enough, although a normal bile duct diameter should be less than 8 mm (5). MRCP has an accuracy of detecting CBD stones surpassing 90%, though there is a clinically significant weakness in the detection of small stones (6). EUS is a minimally invasive endoscopic procedure superior to endoscopic retrograde cholangiography (ERC) in detecting malignant causes of cholestasis and is at least equal to ERC in terms of stone detection (7). EUS-guided ERC has also been reported and may become a rational option (8, 9). Computed tomography has its clinical value above all in unstable patients with high suspicion of underlying malignancy or suspicion of hepatic abscesses.

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In a meta-analysis of a pooled data set of 301 patients, the aggregated sensitivities of EUS and MRCP for CBD stone detection were 93 and 85%, whereas their specificities were 96 and 93%, respectively (10).

3. Severity assessment

There is a wide spectrum of disease courses in acute bacterial cholangitis, ranging from self-limiting to life-threatening with the need to tailor treatment accordingly. An estimated 70% of patients respond to medical treatment comprising supportive and antimicrobial therapy (11). Criteria for severity assessment in the TG13 definition of acute bacterial cholangitis are as follows: grade III (severe): presence of organ dysfunction; grade II (moderate): risk of increased severity without early biliary drainage; and grade I (mild) (12). However, the prospective validation needs to be further studied. G. Paul Wright (13) reported a study using TG13 in a US population. They found that obesity was still a risk factor for the development of acute cholangitis. It was related to severity assessment. So in the future, more factors may be involved for severity assessment.

4. Treatment

Treatment is directed at the two main pathophysiologic components of acute cholangitis, biliary infection and obstruction. Patients with severe disease indicators or significant comorbidities are to be admitted to the intensive care unit.

4.1. Antibiotic Treatment

Most pathogens relevant to cholangitis initiation and perpetuation are derived from gastrointestinal microbiota including Gram-negative enteric bacteria and enterococci. Administration of antibiotic agents should be initiated empirically as early as possible in any patient with a clinical suspicion of cholangitis. If there are signs of septic shock as outlined in the Surviving Sepsis Campaign guidelines, antibiotics should be administered < 1 hour, otherwise < 4 hours for definitive diagnostic studies, and in any event before drainage procedures are performed (14).

The TG13 working group has issued expert opinion based recommendations concerning antibiotic usage in acute bacterial cholangitis (15). The importance of the quality of biliary drainage is highlighted by another study demonstrating that, in the setting of successful ERC drainage, the clinical results were the same after 3 versus 5 days of antibiotic treatment (16). In contrast, in the presence of residual stones or ongoing biliary obstruction, antimicrobial treatment should be extended until the resolution of the anatomical alteration.

Concerning bile cultures, which have been reported to be positive in the range of 59-93%, TG13 recommends

acquisition of bile samples for microbial testing at the beginning of any drainage procedure (15). In contrast, the rate of positive blood cultures in the cholangitis population is about 21-71%. Since the results of blood cultures usually do not affect clinical management and outcomes, routine blood cultures remain a matter of controversy.

There are laboratory and clinical data showing that antimicrobial agents secreting into bile had a better effect. Thus theoretically, biliary secreted antibiotics may be better than non-secreted antimicrobial compounds (17-19).

4.2. Endoscopic and surgical Treatment

Previously, before effective biliary drainage procedures and more potent antibiotic agents became available, the mortality of acute severe cholangitis nearly approached 100% with conservative treatment, however it has now declined to 2.7-10% (20), highlighting the need for the removal of biliary obstruction as the source of ongoing infection in acute bacterial cholangitis. Biliary drainage can be achieved in multitude ways, e.g. ERC, percutaneous transhepatic cholangiography (PTC), EUS-guided drainage, or surgical drainage. There are various endoscopic transpapillary options available, including biliary stent or nasobiliary drain placement above the obstruction site, all of which have appropriate indications corresponding to disease severity and clinical context (21). Stenting has an equal effectiveness compared to nasobiliary drainage; however, it is associated with improved patient comfort, while the nasobiliary tube has the potential advantage of repeated bile aspiration for microbiologic analysis, flushing, and cholangiographic evaluation.

Overall, endoscopic sphincterotomy and stone extraction have been reported to be successful in more than 90% of cases, with adverse event rates close to 5% and mortality rates < 1% (22). After failure of primary wire-guided biliary cannulation, sphincterotomy or percutaneous transhepatic drainage procedures, may become necessary. However, the complication rates for these more advanced techniques are much higher than for standard procedures (23). In few centers, EUS-guided biliary drainage has been introduced as a viable alternative after failed ERC access (24,25). Although this approach requires further standardization and clinical trial validation.

The management of biliary stones is still being debated. Considering the success rates of stone clearance from the CBD, both procedures namely laparoscopic CBD exploration and ERC were similar (91.7 vs. 88.1%) (26). However, Koc *et al.* (27) quoted that the success rate of the laparoscopic common bile duct exploration (LCBDE) + laparoscopic cholecystectomy (LC) group were 96.5%, which was higher than that in the ERC + LC group (94.4%). The overall success

Table 1. Studies comparing early LCBDE and delayed LCBDE

Study (year, reference)	Study type	Subject group	Surgery-related complications	Death	Length of stay (days)	Death
2015 (36)	retrospective case-control	Early	7/32	0	13.34	0
		Delayed	8/41	0	18.32	0
2014 (38)	retrospective case-control	Early	5/94	2/94	3	2/94
		Delayed	8/121	0	3	0
2008 (39)	prospective case-control	Early	6/33	1/33	/	1/33
		Delayed	5/48	0	/	0
2005 (40)	retrospective case-control	Early	1/20	0	2	0
		Delayed	1/24	0	2	0

The results showed that the complication rate between the early and delayed LCBDE didn't have statistical significance ($p > 0.05$ in the four studies respectively). There were 3 deaths in the early LCBDE group of two studies. The 3 patients were all older than 80 years old and all suffered from severe acute cholangitis. We could deem that early LCBDE was suitable for mild and moderate acute cholangitis, but not for severe acute cholangitis because of the high mortality rate.

rate was 88.1% in the LCBDE group and 79.8% in the ECR group ($p = 0.20$) (26). The two procedures for uncomplicated gallstones and CBD stones had nearly similar complication rates, which were 7 and 11.1% ($p > 0.05$), respectively. Noble *et al.* (28) described enhanced attainment rates for laparoscopic versus endoscopic management even for higher-risk patients in complications and hospital stay. Difficulty with cannulation and impacted stones represent the common causes of failure with ERC procedures (28,29). The main reason for unsuccessful clearance following ERC was impacted stones in 13.1% of the patients (26). LC after ERCP is recognized to be troublesome with a higher post complication rate and much more likelihood of conversion to an open approach as a result of inflammation and fibrosis in and around Calot's triangle (30,31). When compared to one-stage laparoscopic CBD exploration, it was found that LC could be very difficult in 33.4% of the patients primarily due to severe adhesions in the ERP group (26).

Additionally, ERC-caused dysfunction of the Oddi sphincter can be permanent and leads to damage of the sphincter barrier, which impedes duodenobiliary reflux (32). Duodenal reflux into the bile duct is associated with a high rate of bacteria colonization following sphincterotomy, which is one of the important mechanisms of biliary duct stone formation. Ding *et al.* (33) supported this mechanism and reported a higher rate of recurrence of CBD stones (9.47% vs. 2.06%) in the ERC + LC group vs. LCBDE group at long-time follow-up approximately up to 3 years. It is essential to deliberate the long-term follow up in order to validate the effectiveness, not only early stone clearance rates. Some studies showed that the duration of postoperative hospital stay in the LCBDE + LC was significantly shorter than that in the ERC + LC group (26,34,35).

In the past few years, comparison between open surgery and laparoscopic surgery were performed (37). The results showed that the prognosis was similar for acute cholangitis, but the length of hospital stay (LOS),

total cost, and complication rate in the laparoscopic group were lower although the average operation time was longer than open surgery.

As laparoscopic skill develops, average operation time was shorter year after year. Some studies (36,38-40) comparing early LCBDE with delayed LCBDE (> 72 h from the onset) were performed (Table 1). The result showed that the complication rate between the early and delayed LCBDE didn't have statistical significance ($p > 0.05$ in the four studies respectively). However, there were 3 deaths in the early LCBDE group while no deaths occurred in the delayed LCBDE group. The 3 patients were all older than 80 years old, and all suffered from severe acute cholangitis. We can deem from the 4 studies that early LCBDE was suitable for mild and moderate acute cholangitis, but not for severe acute cholangitis because of the high mortality rate. However, there were still a few experts trying to perform emergency LCBDE for severe acute cholangitis (38,39). Some even performed primary closure of the common bile duct in emergency LCBDE (39). Though, it was quite debatable.

5. Conclusion

EUS and MRCP were both effective imaging tests for CBD stones. More factors *e.g.* obesity may be involved for severity assessment. Initiation of broad-spectrum antibiotics addressing the typical Gram-negative enteric bacteria spectrum and early biliary drainage are the therapeutic mainstay options. Early LCBDE is also an option for stone-related non severe acute cholangitis.

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